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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/611,835	07/07/00	STOCKWELL B	50164/002002

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EXAMINER	
KOROMA, B	

ART UNIT	PAPER NUMBER
1627	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/611,835	STOCKWELL ET AL.	
	Examiner	Art Unit	
	Barba M. Koroma	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *13, 19, 25-27, 36, 45-47 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14-18, 20-24, 28-35, 37-44, 48-51, 53-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicant's request for extension of time filed on 3/26/01 and entered in paper No. 3, and election without traverse of group I, filed on 3/26/01 and entered in Paper No. 4 is acknowledged. Applicant elected the following species for prosecution on the merits: test element: lung cancer cell line; detection step: cell proliferation; and combination: compounds. The status of the claims is as follows:

2. Claims 1-63 are pending.

3. Upon further consideration, examiner withdraws requirement for election of species based on structural formula of compounds.

4. Claims 25-27, 45-47, withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 4.

5. Claims 13, 19, 36, and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 4.

6. Claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51 and 53-63 are currently being examined in this application.

Claim Rejection 35 USC 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51 and 53-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for test element, lung cancer cell line, does not reasonably provide enablement for identities of test entities, combinations of compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors used in determining undue experimentation are as set forth In re Wands, 858 F.2nd 731, 8 USPQ2d 1400 (Fed. Cir 1988) and an undue experimentation analysis. See MPEP §§2164-2164.08(c). The factors to be considered include: quantity of experimentation necessary; the amount of guidance presented; the presence or absence of working examples; the nature of the invention; the state of the prior art; the predictability of the art; and the breadth of claims.

8. It is the perspective of the examiner that overall, the rationale or utility of the claimed invention is adequately supported in the specifications. However, the specification does not provide clear support for the claims listed above. Such inadequacy is deemed an invitation to undue experimentation on the part of one skilled in the art to successfully practice the invention as claimed. For example, the specification does not specify the compounds to be tested. The use of such compounds would qualify or further substantiate the effectiveness of the methods claimed. This suggests further that it would require the testing of an excessive amount of compounds to determine which "natural" compounds fit the description of combinations as claimed. In addendum, no examples were given of non-polymeric compounds (see page 7, 3rd paragraph) in the specifications. It would require trial-and-error to determine what constitutes 'natural' non-polymeric compounds as claimed. As a corollary, the amount of guidance necessary to expedite successful practice of the instantly claimed invention is inadequate. Case in point, the expression "a second set of compounds" on page 32, second paragraph - line 4 of example 2, is non-enabling due to lack of specific reference to the compounds. These issues when viewed from the position of the prior art which is rife with examples of methods of screening multiple drug compositions (see art rejections below), necessitates a significant amount of experimentation on the part of a skilled worker to practice the invention as claimed. In addition, the art can be regarded as highly evolving, which means that it would require a clear and detailed iteration of steps (including identification of test entities) in order for the specification to be sufficiently enabling.

This rejection is based on scope of enablement which means while applicant may have provided sufficient detail regarding the assay to be used (test element) in order to test the

efficacy of candidate combination of compounds, specification has not provide sufficient information to one skilled in the art regarding the test entities or compounds. Such information for it to be adequate would include reference to compounds by name. Referring to compounds by name e.g. sodium chloride, magnesium sulfate, or Cephalosporin C would be more helpful in the practice of such an invention, than to refer to them merely as 'a set of compounds' as stated above. Baring mention of specific names or identities, one skilled in the art would find it difficult, if not impossible, to practice the claimed invention with any reasonable chance of success, because it would require trial-and-error to determine which entities or compounds applicants intend to qualify as compounds, as claimed.

These limitations are further compounded by the breadth of the claims which, as they stand, do not render sufficient guidance to a skilled artisan. In general, due to lack of enabling information in the claims and specifications as stated above, one skilled in the art would not be able to successfully practice the claimed invention.

Claim Rejection 35 USC 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 11, 17, 18, 34, 35, 51, 60-62, are rejected under 35 U.S.C. 102(b) as being anticipated by **Lam et al (July 22, 1997, US Patent 5,50,489).**

The claims are drawn to a method of screening two-entity or higher combinations for biological activity in a combinatorial array where combinations of said spatially addressable entities (compounds) are contacted with a test element (human cancer cell), for identifying entities that cause an effect on said property of test element that is different from the effect of an entity of the combination by itself.

Lam et al discloses a library of bio-oligomers (reads on claims 18, 35, and 51) of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers. The reference discloses methods of identifying bio-oligomers from a library that demonstrate desired characteristics such as binding, bioactivity and catalytic activity (abstract). In a further embodiment, subunits of peptides that confer useful chemical and structural properties will be chosen (column 11, paragraph 6, line 1-2) with each peptide synthesized from one 'bead' (column 11, 2nd paragraph, lines 7-9). The reference discloses a population of (prokaryotic and eukaryotic) cell lines primary or maintained in culture (reads on claims 2, 3, 4, and 11) in a single cell suspension is layered over liquid medium or a semi-solid matrix containing a random bio-oligomer library. In one embodiment, this procedure is carried out in 96 well-microwell tissue culture plates with one or more beads per well plus the cell suspension (reads on claims 1, 28, 29, 48, 60, and 61). Since each bead represent a unique entity, more than one per well represents multiple combinations per well. In another embodiment, a barrier matrix or 'cookie-cutter' is applied to the suspension of cells and the beads of a library to create individual chambers. A proportion of peptide on each bead is linked with a water cleavable or

photocleavable linker. Sufficient peptide can be released to exert a biological effect while enough peptide still remains linked to the bead for sequencing. The cell suspension may be in solution or may be itself be in a semi-solid matrix. After a suitable incubation period, the cell population is examined for growth or proliferation, e,g. by identification of colonies (column 21, 4th paragraph, lines 1-19). Beads releasing peptide which either stimulated or inhibited cell growth would then be recovered and sequenced with the identified peptide sequences (column 22, 1st and 2nd paragraphs) (reads on claims 1, 28, 48 and 60). Lam teaches fluorescent assays (line 6-8, column 174th paragraph), whole cell membrane bound receptor assay (3rd paragraph, column 19) which reads on claim 5.

Lam et al is a competent prior art because it discloses a method of screening which involves a combination of polymers or compounds with the objective of determining which combination exerts a desired characteristic such as altered rate of cell proliferation.

11. Claims 1, 11, 17, 18, 28, 29, 35, 48, 51, 60-62, are rejected under 35 U.S.C. 102(b) as being anticipated by **Gallop et 1994. (Gallop et. al. Applications of combinatorial technologies to drug discovery. Background and peptide combinatorial libraries. J. Med. Chem. 37:1233-1241. 1994).**

The claims are drawn to a method of screening two-entity or higher combinations for biological activity in a combinatorial array where combinations of said spatially addressable entities (compounds) are contacted with a test element (human cancer cell), for identifying entities that cause an effect on said property of test element that is different from the effect of an entity of the combination by itself.

Gallop et al discloses that the generation of molecular diversity using strategies that covalently connect together members of a set of chemical building blocks in all possible combinations represents a revolution in multiple synthesis. Parallel development of a variety of new high throughput screening methodologies has made evaluation of these combinatorial libraries in biological assays both practical and efficient. The various technologies that have emerged for generating and screening peptide libraries may have fundamentally distinguished by the format in which the diversity is presented (tethered versus soluble libraries; physically segregated ligands versus mixed pools) (page 1242, 3rd paragraph, lines 1-21).

Gallop et al also discloses a split synthesis algorithm method that is readily available and adapted for generating equimolar mixtures of soluble peptides screened in a variety of competition binding or functional bioassays. These hexamer libraries consist of sets of sublibraries that are conveniently prepared by the tea-bag technique. Active peptides are identified from dual position libraries by an iterative process of screening and sublibrary resynthesis in a manner that is completely analogous to the mimotope resolution strategy. All possible combinations of amino acids with activity exceeding some threshold level are then prepared and tested to identify explicit sequences with potent activities (page 1245, 2nd paragraph, lines 1-31). By extending the number of combinations tested to an 'all possible' number, this statement reads on claims with limitations exceeding few combinations (e.g. claims 28, 29, 48, and 60).

The disclosures of Gallop et al read on the instantly claimed invention because it describes a method of screening which utilizes combinations of amino acid entities, the objective of which is to identify combinations with desirable bioactivity.

Claim Rejection 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims1-12, 14-18, 20-24, 28-35, 37-44, 48-51, 53-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lam et al (July 22, 1997, US Patent 5,50,489)**, in view of **Javonovich et al. May 26, 1998. US Patent 5,756,304)** and further in view of **Schultz (US Patent 5985356).**

The claims are drawn to a method of screening two-entity or higher combinations for biological activity in a combinatorial array where combinations of said spatially addressable entities (compounds) are contacted with a test element (human cancer cell), for identifying entities that cause an effect on said property of test element that is different from the effect of an entity of the combination by itself.

The teachings of Lam, Javonovich and Schultz in combination read on the above-listed claims as follows.

Lam et al teaches a library of bio-oligomers of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers. This aspect of the reference reads on claims 18, 35, and 51. Lam et al teaches methods of identifying bio-oligomers from a library that demonstrates desired characteristics such as binding, bioactivity and catalytic activity (abstract). In a further embodiment, subunits of peptides that confer useful chemical and structural properties are chosen (column 11, paragraph 6, line 1-2) with each peptide synthesized from one 'bead' (column 11, 2nd paragraph, lines 7-9). The reference also teaches a population of (prokaryotic and eukaryotic) cell lines primary or maintained in culture in a single cell suspension is layered over liquid medium or a semi-solid matrix containing a random bio-oligomer library. This aspect reads on claim 11. In one embodiment, this procedure is carried out in 96 well-microwell tissue culture plates with one or more beads per well plus the cell suspension (reads on claims 1, 28, 29, 48, 60, and 61). A barrier matrix or 'cookie-cutter' is applied to the suspension of cells and the beads of a library to create individual chambers. A proportion of peptide on each bead is linked with a water cleavable or photocleavable linker. Sufficient peptides can be released to exert a biological effect while enough peptides still remain linked to the bead for sequencing. After a suitable incubation period, the cell population (in solution suspension) is examined for growth or proliferation, e.g. by identification of colonies (column 21, 4th paragraph, lines 1-19). Beads releasing peptide which either stimulated or inhibited cell growth would then be recovered and sequenced with the identified peptide sequences. Beads from wells with biological activity are sequenced and each sequence prepared and tested to determine which of the sequences demonstrate biological activity (column 22, 1st and 2nd paragraphs) (reads on claims 1, 28, 48 and 60).

Lam et al does not teach robotics or inkjet technology as claimed in claims 14, 42, 44, 57, and 59. However, Javonovich teaches robotics and Schultz et al teaches inkjet printing technology as applied to combinatorial chemistry art (please see below for details).

Jovanovich teaches a screening method in a single or panel of target compounds screened against a wide variety of micro organisms with the goal being to "identify target compound(s) of interest" (column 13, 2nd paragraph, lines 1-12). Jovanovich et al teaches a robotic screening of 96-microwell plates using BioMek 1000® equipment as a completely automated system (columns 7, last paragraph; column 8, 3rd paragraph).

Schultz et al teaches methods and apparatus for the synthesis and parallel analysis of novel materials having useful properties (abstract). The reference teaches a solution-dispensing *apparatus such as is commonly employed in the inkjet-printing field. Such inkjet dispensers include pulse pressure type, bubble jet type, and slit jet type*. In an inkjet dispenser of the bubble type, bubbles are generated with a resistance device embedded in a nozzle, and ink is jetted by using the force due to the expansion of a bubble (column 20, 4th paragraph, lines 1-20).

Thus, one skilled in the art would have been motivated at the time the invention was made to successfully combine the screening of two-or-more-entity combinations taught by Lam et al with the robotic screening technology taught by Javonovich, and the inkjet-microfluidics technology taught by Schultz et al.

One skilled in the art would have been expected to have a reasonable chance of success because of the teaching of Javonovich that "methods currently available for selection are very time-consuming, laborious, and not suitable to large-scale screening..," and that "what is needed

is an *apparatus and method* for providing a robotic system to automate large scale screening.." (column 6, 3rd paragraph, lines 1-4).

One skilled in the art would have been expected to adopt (with a reasonable chance of success) inkjet technology taught by Schultz et al, because of the teaching of Schultz et al, that, "there exists a need in the art for a more efficient, economical and systematic approach for the synthesis of novel materials and for the screening of such materials for useful properties". (column 2, lines 1-4).

14. No claim is in condition for allowance

15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

16. All inquiries pertaining to this case should be directed to ***Barba M. Koroma.*** This examiner can normally be reached at: **703 305 1915, at *9:00am to 5:00pm, Monday through Friday.***

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, PhD, can be reached at: 703 308 2439. The phone number for the organization where this application or proceeding is assigned is: 703 308 2742. Any inquiry of a general

nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is: 703 308 1235.

Barba M. Koroma, Ph.D
Patent Examiner
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J. Venkat

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